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(71) Applicant: VIROTEX CORPORATION [US/US]; Suite 350, 4200 Research Forest Drive, The Woodlands, TX 77381 (US).

(72) Inventor: OSBORNE, David, W.; 19 Quiet Oak Circle, The Woodlands, TX 77381 (US).

(74) Agent: PATTERSON, Melinda, L.; Arnold, White & Durkee, P.O. Box 4433, Houston, TX 77210 (US).

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(57) Abstract

A topical semisolid composition for use on mucosal membranes comprising one or more hydrophilic polymers suspended in a non-aqueous matrix. The composition may be combined with a therapeutic agent to assist in healing mucosal lesions.

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IMPROVED TOPICAL CARRIERS FOR MUCOSAL APPLICATIONS

This present invention relates to topical carrier compositions which are capable of adhering to mucosal surfaces and which resist dissolution and/or erosion upon exposure to moisture. More specifically, the present invention relates to topical carrier compositions which may be used as vehicles for therapeutic agents in mucosal lesion treatments.

Many mucosal diseases are characterized by lesions localized on mucosal surfaces, particularly oral mucosal membranes such as buccal and gingival epithelium. These diseases include lichen planus, Behcet's syndrome, and canker sores. More generalized conditions, such as oral candidiasis, are also frequently encountered.

While topically-applied drug therapies are available for treatment of these conditions, the effectiveness of these drugs is typically hampered by the rapid dissolution of the carrier matrix. In fact, most preparations utilized for application to the oral mucosa are removed by saliva and the mechanical action of routine mouth movements within a few seconds of application. This does not allow sufficient time for the topically-applied therapeutic agent to be released from the formulation and delivered to the mucosal site. Consequently, a need exists for carrier compositions which are capable of remaining at the site of application for extended periods of time.

The present invention comprises a topical semisolid composition for use on mucosal membranes. The composition comprises one or more hydrophilic polymers suspended in a non-aqueous matrix. In one embodiment of the present invention, the hydrophilic polymer is cellulose gum, hydroxyethylcellulose, cross-linked acrylic acid polymers, PVM/PA copolymers, or combinations thereof.

In another embodiment of the present invention, the non-aqueous matrix is petrolatum, mineral oil, or combinations thereof. In still another embodiment, the non-aqueous matrix is a triglyceride. In another embodiment the non-aqueous matrix is a natural oil such as olive oil, peanut oil, almond oil, corn oil, or vegetable oil.

In a preferred embodiment of the present invention, the composition further comprises a therapeutic agent such as a local anesthetic, a corticosteroid, an antimicrobial or an antifungal.

The present invention is directed to novel, topical carrier compositions which may be applied to mucosal surfaces wherein the compositions are capable of forming a multi-layered coating over the treated mucosal site upon initial contact with moisture, wherein the coating comprises a hydrated adhesive layer proximate the mucosal surface, a non-aqueous matrix layer, and a hydrated top-coat film, and wherein said coating resists dissolution and/or erosion upon further contact with moisture.

The carrier compositions of the present invention comprise suspensions of rapidly hydrating hydrophilic polymers in non-aqueous matrices. As formulated, these compositions exhibit non-adhering, gel-like properties. However, upon contact with water, the exposed surfaces of the compositions are quickly hydrated to form a sealed, water-retardant film. The film resists further hydration within the non-aqueous matrix. Furthermore, if the composition is contacted with a moist

surface, an adhesive, water-retardant seal is formed between the composition and the surface such that the composition becomes fixedly disposed on the site. Thus, the present invention is highly effective in both adhering to mucosal surfaces and resisting dissolution and/or erosion upon exposure to moisture, due to the water-retardant film which forms around the carrier composition.

The hydrophilic polymer constituent of the compositions of the present invention may comprise, for example, calcium/sodium PVM/MA copolymer (commercially available as Gantrez MS-955 produced by GAF). Cellulose Gum (commercially available as CMC produced by Aqualon), hydroxyethylcellulose (commercially available as Natrosol produced by Aqualon), cross-linked acrylic acid polymers (such as the commercially available product Carbopol, produced by Goodrich), or PVM/MA copolymer (such as the commercially available product Stabileze, produced by ISP), or any combinations thereof.

The non-aqueous matrix component of the compositions of the present invention may comprise petrolatum, mineral oil, triglyceride, or a mixture of oils derived from natural sources, i.e., olive oil, peanut oil, almond oil, corn oil, or vegetable oil. The non-aqueous matrix may also comprise a mixture of the above compounds.

The hydrophilic polymer or combination of polymers as described above is preferably present in an amount equal to 2% to 40 weight percent of the overall composition. The nonaqueous matrix comprises the remainder of the formulation, i.e., about 60% to 98% by weight.

The present invention may be used as a carrier for therapeutic agents, especially medicinal agents used in the treatment of mucosal lesions. Examples of typical therapeutic agents include local anesthetics, corticosteroids, destructive

therapy agents, antimicrobials and antifungals. Some preferred concentrations of therapeutic agents are as follows:

For local anesthetics such as tetracaine, tetracaine hydrochloride, lidocaine, lidocaine hydrochloride, dyclonine hydrochloride, dimethisoquin hydrochloride, dibucaine, dibucaine hydrochloride, butamben picrate and pramoxine hydrochloride a preferred concentration is about 0.025% to 5% by weight of the total composition. For anesthetics such as benzocaine a preferred concentration is about 2% to 25% by weight;

For corticosteroids, such as betamethasone dipropionate, fluocinolone acetonide, betamethasone valerate, triamcinolone acetonide, clobetasol propionate, desoximetasone, diflorasone diacetate, amcinonide, flurandrenolide, hydrocortisone valerate, hydrocortisone butyrate, and desonide, a preferred concentration is about 0.01% to 1.0% by weight. Corticosteroids such as hydrocortisone or methylprednisolone acetate are preferably present in concentrations of about 0.2% to about 5.0% by weight.

Destructive therapy agents such as salicylic acid or lactic acid would preferably comprise about 2% to about 40% by weight of the composition. Cantharidin is preferably utilized in a concentration of about 0.1% to about 2.0%, and podophyllin would preferably be used in a concentration of about 5% to about 30% by weight.

Some typical antimicrobials and antifungals and their preferred weight concentrations include: silver sulfadiazine (0.2% to 5.0%), oxiconazole nitrate (0.1% to 5.0%), ciclopirox olamine (0.1% to 5.0%), ketoconazole (0.1% to 5.0%), miconazole nitrate (0.1% to 5.0%), butoconazole nitrate (0.1% to 5.0%), neomycin (0.1% to 2.0%), gramicidin (0.01% to 0.1%), chlortetracycline hydrochloride (1.0% to 5.0%), meclocycline sulfosalicylate (0.2% to 4.0%),

oxytetracycline (1.0% to 5.0%), and tetracycline hydrochloride (0.05% to 5.0%). Additionally, about 2,000 to about 10,000 units of Polymyxin B, or about 200 to about 1,000 units of bacitracin may be utilized.

The above recitations of typical therapeutic agents are for illustration only, and should not be considered a limitation on the scope of the present invention. Those of skill in the art will recognize other types of therapeutic agents that may be utilized, and the preferred concentrations of those other agents.

In applications utilizing therapeutic agents, the agents may be combined with the non-aqueous matrix of the present invention by any means known to those skilled in the art. Thereafter, the therapeutic topical composition may be applied to particular mucosal sites requiring treatment. Upon contact with water, such as from saliva, the composition will adhere to the mucosal site and form a protective, water-retardant film on all surfaces exposed to the moisture such that the therapeutic agents within the composition are available for delivery to the mucosal site for an extended period of time.

As a preferred embodiment, the carrier compositions of the present invention may be combined with any local anesthetic known in the art for treatment of canker sores and/or lesions produced by Behcet's syndrome. As another preferred embodiment, the carrier compositions may be combined with corticosteroid or cyclosporin A for the treatment of lichen planus.

To further illustrate the present invention, but not by way of limitation, the following examples are provided.

Example 1

10% Mineral Oil, 4-20% Gantrez MS-955, 4-20% Cellulose Gum, 50-82% White Petrolatum.

Example 2

4-10% Natrosol, 4-10% Gantrez MS-955, 4-10% Cellulose Gum, 70-88% White Petrolatum.

Example 3

10% Mineral Oil, 4-20% Gantrez MS-955, 4-10% Cellulose Gum, 70-82% White Petrolatum.

Example 4

4-10% Carbopol, 4-10% Gantrez MS-955, 4-10% Cellulose Gum, 70-88% White Petrolatum.

Those skilled in the art will recognize that, while specific embodiments have been illustrated and described, various modifications and changes may be made without departing from the spirit and scope of the invention.

CLAIMS:

1. A topical semisolid composition for use on mucosal membranes comprising one or more hydrophilic polymers suspended in a non-aqueous matrix.

2. The composition of claim 1 wherein the hydrophilic polymer is selected from the group consisting of cellulose gum, hydroxyethylcellulose, cross-linked acrylic acid polymers, PVM/MA copolymers, or a combination thereof.

3. The composition of claim 1 wherein the non-aqueous matrix is petrolatum, mineral oil, or a combination of petrolatum and mineral oil.

4. The composition of claim 1 wherein the non-aqueous matrix is a triglyceride.

5. The composition of claim 1 wherein the non-aqueous matrix is selected from the group consisting of olive oil, peanut oil, almond oil, corn oil, or vegetable oil.

6. The composition of claim 1 further comprising a therapeutic agent.

7. The composition of claim 6 wherein the therapeutic agent is a local anesthetic.

8. The composition of claim 7 wherein the local anesthetic is suitable for treatment of canker sores or Behcet's syndrome.

9. The composition of claim 6 wherein the therapeutic agent is a corticosteroid.

10. The composition of claim 9 wherein the corticosteroid is suitable for the treatment of lichen planus.

11. The composition of claim 9 wherein the corticosteroid is cyclosporin A.

12 The composition of claim 6 wherein the therapeutic agent is an antimicrobial or antifungal.

INTERNATIONAL SEARCH REPORT

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A. CLASSIFICATION OF SUBJECT MATTER

IPC(6) : A61K 31/74
US CL :514/78.02, 78.03, 78.05, 78.06, 78.07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/78.02, 78.03, 78.05, 78.06, 78.07

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN; COMPOUNDS, ANTIVIRAL AND ANTIBIOTIC METHODS OF USE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GENNARO ET AL, "REMINGTON'S PHARMACEUTICAL SCIENCES" , published 1985 by Mack Publishing Co. (Easton PA.), pages 805, 1285, 1295, 1298, 1301, 1302.	1-12
Y	WINDHOLZ ET AL, "THE MERCK INDEX" published 1982 by MERCK & CO., Inc. (RAHWAY, NJ), numbers 7661, 5310, 2748, 2510, 212.	1-12
Y	CHEMICAL ABSTRACTS, Volume 112, Number 11, issued 12 MARCH 1990, YANGI ET AL, "DESTABILIZATION OF HERPES SIMPLEX VIRUS TYPE 1 VIRIONS BY LOCAL ANESTHETICS, ALKALINE pH, AND CALCIUM DEPLETION", page 63, column 1, Abstract No. 112:91623a.	6-8, 10

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CHEMICAL ABSTRACTS, Volumn 117, No, 19, issued 07 September 1992, Popp , "ANTIWART COMPOSITIONS CONTAINING KERATOLYTIC AGENTS" page 62, column 2, Abstract No. 117:97356r.	6-8, 10